CORTICOSTERONE MEDIATES THE EFFECTS OF CHRONIC STRESS ON THEILER'S VIRUS IN MICE

A Senior Honors Thesis

by

DANIELLE MARIE SATTERLEE

Submitted to the Office of Honors Programs
& Academic Scholarships
Texas A&M University
In partial fulfillment of the requirements of the

UNIVERSITY UNDERGRADUATE
RESEARCH FELLOWS

April 2001

Group: Psychology 2

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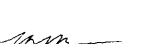
Approved as to style and content by:



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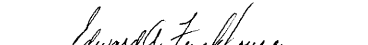

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April 2001

Group: Psychology 2

ABSTRACT

Corticosterone Mediates the Effects of

Chronic Stress on Theiler's Virus in Mice. (April 2001)

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Theiler's Murine Encephalomyelitis Virus in mice is a clinically relavant model of multiple sclerosis (MS) since the current hypothesis is that a viral infection may be the initiating event in the development of MS. Chronic restraint stress profoundly affects vulnerability to the acute phase of Theiler's virus. This study confirms that restraint results in higher mortality rates, more severe clinical signs and decreased body weights in mice restrained and infected with Theiler's virus compared to nonstressed-infected mice. Two experiments identified the mediator of these effects as corticosterone, a stress hormone released by the HPA axis. The first experiment found that restraint stress elevated corticosterone levels, and the second experiment found that administration of exogenous corticosterone produced immune suppressive effects similar to restraint (mortality, increased symptomatology, decreased body weight).

TABLE OF CONTENTS

LIST OF FIGURES

1. Introduction

A growing body of evidence supports the idea that the central nervous system (CNS) and the endocrine system interact to modulate immune system activity. The effects of stress on immune function are a good example of this concept. One means, by which physical and psychosocial stressors activate the hypothalamic pituitary adrenal (HPA) axis. Stressors cause the release of corticotropin releasing hormone (CRH) from the hypothalamus. This release then stimulates the pituitary gland to release adrenocorticotropin hormone (ACTH). ACTH circulates in the bloodstream and stimulates the adrenal cortex to release glucocorticoids, which then influence the activity of the various immune effector cells directly.

The influence of stress on the immune system depends on the stressor's duration. Acute stress stimulates the immune system by increasing production and activity of immune cells and then redistributing them to the site of infection (Dhabar & McEwen, 1996). In contrast, chronic stress suppresses immune responses and makes the organism more vulnerable to infection. Evidence suggests that the stress hormone products of the HPA axis mediate this effect. For example, studies have shown chronic stress increases susceptibility to herpes simplex and influenza viruses in mice and that this effect is mediated by the stress hormone corticosterone (DeLano, & Mallery, 1998; Sheridan, Dobbs, Jung, Chu, Konstantinos, Padgett, & Glaser,

This thesis follows the style and format of the *Journal of Neuroimmunology*

1998). These studies found that restraint stress suppressed immune responses including natural killer (NK) cell activity, the production of cytokines (IL-1α), lymphodenopathy and mononuclear cell trafficking. Glucocorticoids produced by the HPA axis were shown to mediate this stress-induced immune suppression (Sheridan 1998).

Stress has been implicated as a contributing factor to the onset and progression of several autoimmune diseases in humans, including multiple sclerosis (MS). Victimizing approximately 1 in 2000 people in the United States, MS is the most common demyelinating disease of the CNS. The cause of the disease is presently unknown, although viral infection in early adulthood is thought to be an initiating event. Anecdotal reports suggest that life stress frequently triggers the development of MS symptoms (Grant 1993). Recent studies using standardized assessment of life events substantiate the idea that psychological stress precedes both the onset and exacerbation of MS symptoms in 70 to 80% of cases (Warren et al., 1982). Psychological stress can be used to predict subsequent development of brain lesions in patients with relapsing forms of MS (Mohr, Goodkin, Boudewyn, Huang, Marietta, Cheuk, & Dee, 2000). The application of an acute stressor to healthy subjects as well as MS patients has been shown to alter immune function in such a way that it could potentially exacerbate autoimmune disease (Mohr, Goodkin, Bacchetti, Boudewyn, Huang, Marietta, Cheuk, &

Dee, 2000). However, studies investigating the effects of stress on MS are few and their results remain controversial.

Experimentation using animal models of MS, such as Theiler's murine encephalomyelitis virus (TMEV) in mice, supports the contention that stress plays a role in the disease. Theiler's virus is a picornovirus, which in nature causes an acute enteric infection and occasionally paralysis. In order to cause demyelination similar to MS, TMEV must establish a persistent infection in the CNS (Welsh, Blakemore, Tonks, Borrow, & Nash, 1989). The effects of stress on the pathogenesis of Theiler's virus infection in CBA mice were explored by Campbell, et al. (in press). In their study, restraint stress suppressed the immune system and severely exacerbated the TMEV infection. Infected-restrained mice had a higher incidence of clinical symptoms and mortality than the infected-nonstressed (control) mice. Immunosuppression was evidenced by the reduced number of circulating lymphocytes, thymic atrophy, and higher viral titers present in stressed-infected mice. These findings suggest that these mice were unable to clear the virus from the CNS as effectively as mice in the infected-control group were. (Campbell et al., in press).

Previous studies have implicated viral infections as an important initiating event in the etiology of MS. According to the current theory, viruses that trigger MS are cleared from the general population, but in a few vulnerable individuals, they may be able to establish a persistent infection

eventually resulting in the chronic demyelination characteristic of MS. Stress-mediated immunosuppression could be one factor contributing to individual vulnerability to this virus. However, scientific literature on this subject is lacking. As a model of MS, TMEV is unique because it consists of both an acute encephalitis phase, comparable to the initial viral infection, and a chronic phase, comparable to the autoimmune demyelinating process. The present study focuses on how stress effects the acute phase of TMEV in an effort to gain insight into the virus that hypothetically triggers MS.

The most likely candidate for the mechanism that mediates stress-induced immune suppression in TMEV is elevated corticosterone resulting from prolonged activation of the HPA axis. In the present study, two experiments explored the role of corticosterone in the acute phase of TMEV infection. The first experiment was designed to establish a relationship between elevated levels of corticosterone and restraint stress. The objective of the second experiment was to determine if corticosterone was sufficient to create the pathology observed in restrained animals infected with TMEV. In this procedure, exogenous corticosterone was administered without stress.

2. Methods

2.1 EXPERIMENT 1

2.1.1. Subjects

Subjects were 48 three-week old male CBA mice (Harlan Laboratory). The strain was chosen for its intermediate susceptibility to the BeAn strain of

Theiler's virus. Mice were housed six per cage and maintained on a 12-hour light/dark cycle. Food and water was available ad libitum. To habituate the mice to human contact, all mice were handled for a couple of minutes each day for three days prior to the behavioral stress procedures.

2.1.2. Acute Clinical Signs.

Following one week of acclimation to the laboratory and handling, each animal was examined for the development of clinical signs indicative of acute neurological disease twice per week. For each mouse, body weight and clinical score were recorded. The clinical score was based on a numerical scale with zero indicating a healthy animal and higher numbers representing gradually increasing severity of symptoms. Scores were determined by assigning point values to clinical signs of illness and then summing the points for each animal. Subjects received half a point for each of the following: slightly ruffled fur, slightly hunched posture, partial grooming, slight lethargy/weakness, and slightly crusted/sunken eyes; they received one point for exhibiting each of these symptoms to a greater degree (i.e. prominently ruffled fur and prominently hunched). Baseline measures of body weight and clinical score were taken twice during the week prior to stress and infection.

2.1.3. Behavioral Stress Conditions.

Two weeks after arrival and one day prior to infection, -1 post-infection (pi), mice were randomly assigned to either the restraint stress (n=24) or no stress control (n=24) condition. Mice receiving restraint stress were placed in

well-ventilated 60 mL plastic tubes for 12 hours (8 p.m.-8 a.m.) five nights per week for four consecutive weeks. Inside the tube, the mouse could move forward and backward freely, but he could not turn around nor did he have access to food or water. Mice in the no stress control condition remained undisturbed in their home cages. Because previous research showed that food and water deprivation in the absence of restraint did not affect pathology in Theiler's infected mice (Campbell et. al., in press), this group was not included in the present study.

2.1.4. Infection

After the first day of restraint, day 0 pi, half of the mice in the stress and control conditions were anesthetized with metofane and infected intracranially with 5×10^4 p.f.u. of the BeAn strain of Theiler's virus in a volume of 20 µl. The other half were mock infected with 20 µl of PBS.

2.1.5. Bleeding

After acclimation to handling, all mice were bled (150 µl/bleed) on days -5, 1, 2, 7, 16, 24, and 35 pi. Bleeds occurred at the same time of day (8-11 a.m.) by nicking the saphenous vein of the leg. Mice were bled one at a time under a fume hood, less than 10 seconds following removal from the home cage or restraint tube. Blood samples were taken into heparinized tubes, placed on ice, and centrifuged. The serum was stored at -80 C until assayed.

2.1.6. Corticosterone Assays.

Corticosterone levels were measured from these serum samples by radioimmunoassay (ImmuChem Double Antibody Corticosterone RIA Kit, Biomedicals, Inc.).

2.1.7. Statistical Analyses.

Differences in serum corticosterone levels, body weights, and clinical scores were analyzed using a repeated measures analysis of covariance (ANCOVA), entering the baseline measure as a covariate, infection status and behavioral condition as between group factors, and time as a within group factor.

2.2. EXPERIMENT 2

2.2.1. Subjects

Sixteen subjects, housed four per cage, of the same age, sex, and strain as subjects in Experiment 1 were used.

2.2.2. Clinical Signs

Body weights and clinical scores were again recorded twice each week for all mice beginning one week before the initiation of stress and infection.

2.2.3. Exogenous Corticosterone Administration

Mice were randomly assigned to either the corticosterone or no corticosterone control condition. Corticosterone-treated mice (n=8) received 400 µg/mL corticosterone (Sigma Laboratories) in their drinking water with 2% ethanol to keep it in solution (Jellink, Dhabar, Sakai, & McEwen, 1997).

Control mice (n=8) received only 2% ethanol in their water. Timing of corticosterone administration was designed to mimic elevated corticosterone levels produced by the restraint schedule in experiment 1. Mice received the drug at 8 p.m. the day before infection (-1 pi) and it remained in their water bottles for four weeks.

2.2.4. Infection

On day 0 pi, all subjects were anesthetized with metophane and infected intracranially with 5×10^4 p.f.u. of the BeAn strain of Theiler's virus in a volume 20 µl.

2.2.5. Serum Corticosterone Levels--Manipulation Checks

Bleeds were scheduled for days -5, 1, and 15 pi to check that the corticosterone administration was effective. However, the corticosterone condition experienced high and rapid mortality before the third bleed could be performed.

2.2.6. Statistical Analyses

ANCOVA's were performed on body weight and clinical score with the baseline measures used as covariates, treatment condition as a between groups factor, and time as a within group factor.

3. Results

3.1. EXPERIMENT 1

3.1.1. Serum Corticosterone Levels

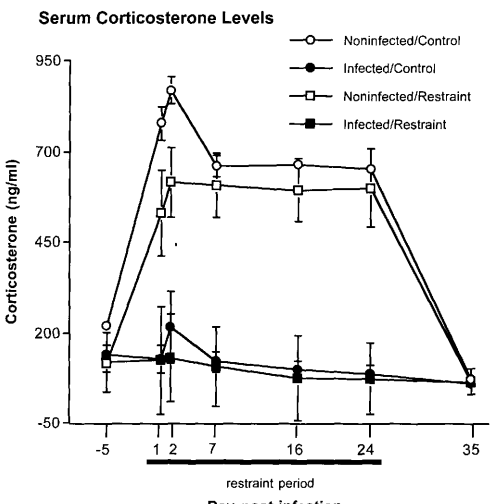

Fig. 1. Mean corticosterone levels (ng/ml) over time for noninfected-control, infected-control, noninfected-restrained, and infected-restrained mice are shown. The black bar indicates the period of restraint.

Blood samples were obtained from all animals to determine the effects of restraint stress and infection on corticosterone levels. A baseline bleed (day -5 pi) occurred four days prior to stress followed by five bleeds (days 1, 2, 7,16, 24 pi) during the stress period and one bleed (day -35 pi) ten days after the cessation of stress. To control for pre-treatment variations in serum corticosterone levels, an Analysis of Covariance (ANCOVA) was performed using baseline corticosterone as a covariate. As Fig. 1 illustrates, restraint stress significantly elevated corticosterone levels in both noninfected and infected animals, F (1,29) = 268.43, p<.0001. The effect of restraint on corticosterone levels did not diminish across the bleeding time points (days 1, 2, 7, 16, 24 pi), F (3, 87) = 2.02, p>.05. There was not a persistent elevation in corticosterone after the termination of restraint stress: the effect of stress was not significant at day 35 pi, F = .98, p>.05.

Infection also produced a significant increase in serum corticosterone in both restrained and control animals, F (1,29) = 5.08, p<.032. However, the interaction between restraint and infection was not significant, F (1,29) = 1.79, p>.05.

3.1.2. Mortality

Fig. 2 depicts survival curves for each of the four conditions. Within the first week following infection, five of the 12 infected-restrained mice died while only one of the 12 noninfected-restrained mice died. No mice died in the control (no stress) conditions.

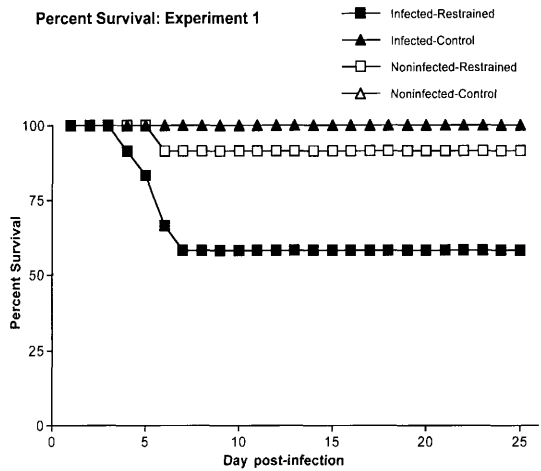

Fig. 2. The percent survival over time is depicted for each of the four conditions.

3.1.3. Clinical Scores

Twice each week, all subjects were examined for signs of illness (ruffled fur, poor grooming, hunching, lethargy, and sunken eyes). Increasing clinical scores represented worsening of these symptoms. Fig. 3 compares the worst clinical scores for each condition during the course of the

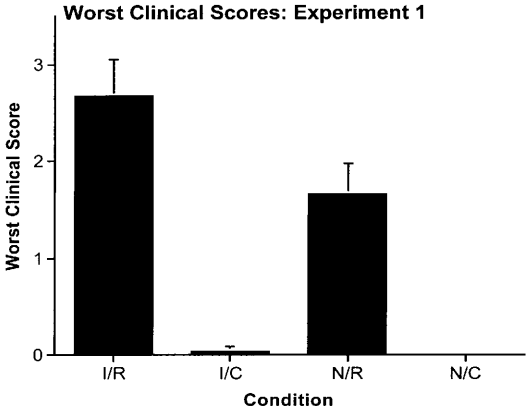

Fig. 3. The mean worst clinical scores are compared for each group: infected-restrained (I/R), infected-control (I/C), noninfected-restrained (N/R), and noninfected-control (N/C).

experiment. The highest clinical scores were exhibited by mice in the infected-restrained animals followed by the noninfected-restrained animals. The control conditions, both infected and noninfected, showed very little sign of disease. An Analysis of Variance (ANOVA) using each animal's worst clinical score showed significant effects of restraint, $\underline{F}$ (1,44) = 77.03, $\underline{p}$<.0001, and infection $\underline{F}$ (1,44) = 4.54, $\underline{p}$<.039. The interaction between stress and infection failed to reach significance $\underline{F}$ (1, 44) = 3.84, $\underline{p}$<.056.

However, a priori planned contrasts were performed based on previous findings (Campell, et al., in press) and revealed that the infected-restrained group was significantly more symptomatic than the other groups combined, F (1,44) = 55.18, p<.0001, and than the noninfected-restrained group, F (1,44) = 8.36, p<.006. 3.1.4.

3.1.4. Body Weights

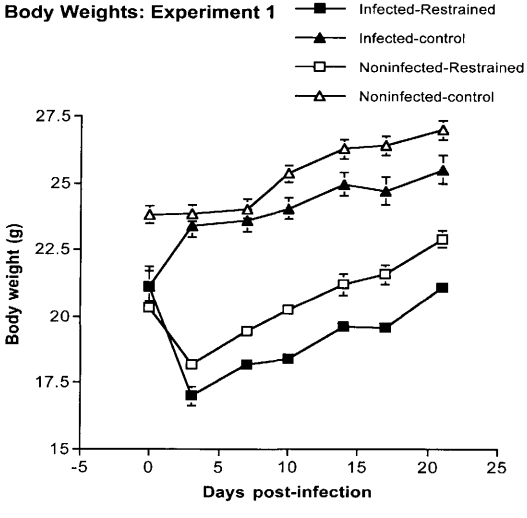

Fig. 4. Body weights (g) are depicted against time for each condition.

As illustrated in Fig. 4, restraint stress and infection both reduced body weight. A sharp decrease in weight of restrained animals occurred on day 3 pi, after which this group was able to recover somewhat. An ANCOVA using baseline as a covariate confirmed that restraint stress, F (1,35) = 248.77, p<.0001, and infection, F (1,35) = 7.57, p<.009, produced significant weight loss over time.

3.2 EXPERIMENT 2

3.2.1. Mortality

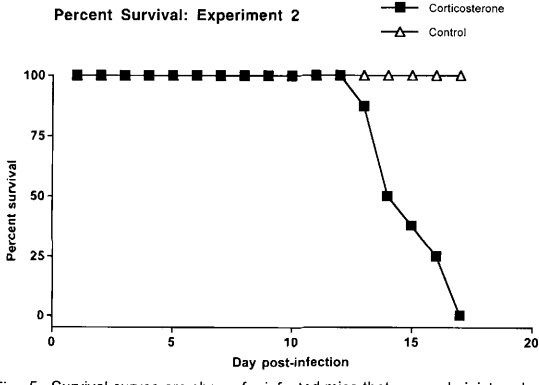

Fig. 5. Survival curves are shown for infected mice that were administered corticosterone and infected control mice.

In this experiment, all mice were infected; half received corticosterone in their drinking water and the other half did not. Corticosterone had a profound impact on the pathology of the virus. The survival curve in Fig. 5 depicts dramatic mortality in the corticosterone-treated group. The mice in this group began to die day 13 pi and reached 100% mortality by day 16 pi while the control mice did not experience any mortality.Fig. 5. All subjects receiving corticosterone died between 13 and 16 days pi. None of the control subjects although also infected died.

3.2.2. Clinical Scores

A comparison of corticosterone-treated and control mice in Fig. 6 illustrates that the clinical symptoms in treated mice began to increase on day 5 pi as the quality of their grooming began to decline. Scores increased rapidly over the next week as mice became very hunched and lethargic. By day 16, they had all died. The control mice never showed any signs of illness.

Analysis of clinical scores with an ANCOVA confirmed that over time corticosterone administration significantly increased clinical scores, F (1,13) = 65.90, p<.0001, and day pi, F (4,52) = 35.88, p<.0001. There was also a significant interaction between day pi and condition, F (4,52) = 35.88, p<.0001.

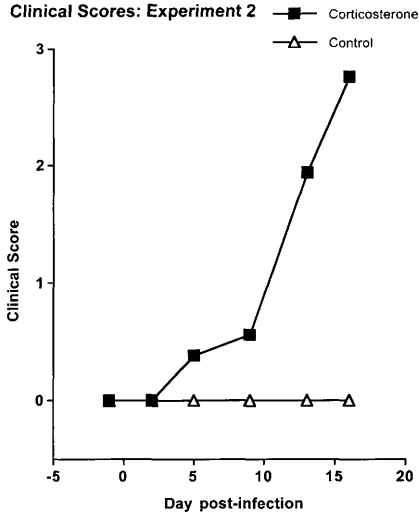

Fig. 6. Clinical scores for the corticosterone-treated and control groups are depicted over time.

3.2.3. Body Weight

Corticosterone administration significantly lowered body weight over time as depicted in Fig. 7. The body weights of control mice increased steadily while weights of the treated mice decreased slowly the first week after infection and then plummeted day 13 pi around the same time that

clinical scores began to increase. An ANCOVA showed a main effect of corticosterone, F (1,6) = 63.36, p<.0002 and an interaction effect between corticosterone and day pi, F (4,24) = 54.51, p<.0001.

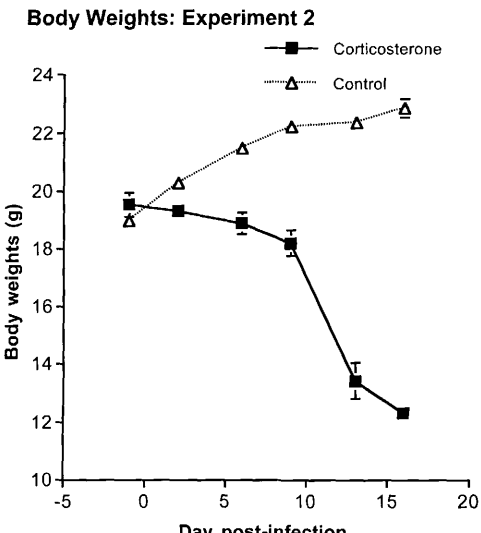

Fig. 7. Body weights for both conditions are represented across time.

4. Conclusions

The results of this investigation show that the effects of restraint stress on the pathogenesis of TMEV in CBA mice are at least partly mediated by elevated levels of corticosterone. In the first experiment, chronic restraint stress increased vulnerability to TMEV as indicated by reduced body weights, increased clinical scores, and higher mortality rates of the infected-restrained mice. Significantly elevated corticosterone levels accompanied this increased symptomatology in the restrained group. In the second experiment, exogenous corticosterone administration produced a similar pattern of results: increased clinical scores and mortality and decreased body weights. Therefore corticosterone appears to be sufficient to produce the pathology observed in restraint-stressed mice infected with Theiler's virus.

This study supports previous findings that chronic restraint stress increases susceptibility to the acute phase of Theiler's virus infection (Campbell et al., in press). Campbell et al. also found increased clinical signs and mortality in infected-restrained mice, although to a greater degree. This previous study resulted in an 80% mortality rate while the present study produced only 42% mortality. The difference in these findings may be explained by the change in the nature of restraint. The present study used less confining tubes, which may not have been as severe of a stressor.

The effect of elevated corticosterone in TMEV appears to be similar to the role of corticosterone in other viruses, such as herpes and influenza in

mice. Elevated levels of corticosterone ensuing from restraint-stress exacerbates these infections by suppressing immune responses including natural killer (NK) cell activity, the production of cytokines (IL-1α), lymphodenopathy and mononuclear cell trafficking (Sheridan, 1998). In influenza and herpes, blocking glucocorticoid receptors with RU486 restored all these immune functions in restrained-infected mice indicating that glucocorticoids produced by the HPA axis are necessary for stress-induced immune suppression (Sheridan 1998). The present study provides evidence that corticosterone is sufficient to create the stress-induced immunosuppression seen in TMEV, but the question of whether it is necessary still remains. Administration of a corticosterone antagonist in conjunction with restraint-stress could answer this question. We attempted this procedure with RU486 (which blocks the effects of corticosterone), but it resulted in mortality most likely due to unckecked inflammation in the CNS. Personal communication with David Padgett and John Sheridan revealed that high mortality also results from using RU486 with an influenza model due to uncontrolled fluid accumulation in the lungs.

Another model of MS in mice, experimental allergic encephalomyelitis (EAE), has been used to study the mechanisms, by which stress impacts autoimmune disease. Chronic restraint stress received prior to infection has been shown to profoundly suppress the clinical and pathological changes of EAE in mice and rats (Whitacre, Dowdell, & Griffin). This effect was partially

reversed by the administration of RU486 in restrained mice confirming that glucocorticoids mediate stress-induced suppression of EAE (Dowdell, Gienapp, Stuckman, Wardrop, & Whitacre, 1999).

Stress influences EAE and TMEV in contrasting ways, due to the differential mechanisms through which the models effect the CNS. EAE is a monophasic disease, mediated by neuroantigen-specific T lymphocytes, which upon encountering the neuroantigen, express proinflammatory lymphokines, eventually recruiting additional specific and nonspecific inflammatory cells and establishing demyelinating lesions (Dal Canto, Melvold, Kim, & Miller, 1995). Glucocorticoids that ensue from activation of the HPA axis by stress inhibit this response and thus reduce symptoms of the disease (Dowdell 1999). In contrast, during the acute phase of TMEV, NK cells and cytokines are important elements of the immune response that are directed at clearing the virus from the animal's CNS. Persistence of the virus in the CNS is required for demyelination to occur in the later chronic phase. Since glucocorticoids are known to suppress these immune cells, this may be why stress increases vulnerablity to the acute phase of Theiler's virus as shown by the present study.

The HPA axis is not the only neuroendocrine pathway that may mediate the effects of stress on Theiler's virus. Stress-induced activation of the sympathetic nervous system (SNS) may also play a significant role. The sympathetic stress response is initiated by the hypothalamus and causes the

release of catecholamines from sympathetic nerve terminals and from the adrenal medulla. Catecholamines, such as noradrenaline, can directly effect immune cells. For example, noradrenaline has been shown to suppress T cell (CD 8) activity (Madden, Sanders, & Felten, 1995), and T cells are an important element of the immune response to TMEV (Welsh, et al., 1987). Although the SNS has not been shown to play a major role in EAE suppression (Dowdell, et al., 1999), the effects of noradrenaline on TMEV have not been investigated. A combination of HPA and SNS activation may underlie the effects of stress on Theiler's virus infection.

Experimentation using animal models of MS reveals that the neuroendocrine mechanisms, by which stress may affect the development of the disease, are complex. Theiler's virus is a valuable tool in illuminating some of these mechanisms since the current hypothesis is that a viral infection early in life, paired with a genetic predisposition, may trigger a secondary misdirected immune response that could be directed either against myelin antigens and/or possible persistent viruses. If this hypothesis is correct, TMEV is a particularly useful model since it allows investigation of the acute phase of viral infection, which may operate similarly to the initial viral agent involved in MS. EAE and the TMEV chronic phase are only comparable to the autoimmune demyelinating disease and do not provide insight into mechanisms of the virus that may trigger this disease.

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Golden Key National Honor Society, 1998-present

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Award for 500 hours of service to the Student Counseling Helpline, 2000

TAMU President's Endowed Scholarship 1997-2001

Honors Student Council 1997-1999

TAMU Merit Plus Award 1997-1998

National Merit Scholar 1997

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